III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1-27 are currently pending in this application. Claims 1-15 and 18-22 were previously withdrawn from consideration as being drawn to a non-elected invention. Solely to expedite prosecution and without prejudice to the applicant's right to seek broader claims in a continuing application, the applicant has canceled claims 1-15 and 18-22 without prejudice. Claims 16, 17, and 23-27 remain at issue. This response is timely filed with an extension of time in the third month.

On page 2 of the official action, the examiner alleged that applicant's amendment to the priority statement in the specification allegedly did not indicate the relationship of the present application to PCT/US01/40835. The applicant has amended the priority information on page 1, line 2 of the specification to provide the relationship between the instant application and PCT/US01/40835. Specifically, the instant application is the U.S. national of PCT/US01/40835. Please note that the applicant has further amended the specification at paragraph 0005 to correct typographical errors regarding U.S. Patent No. 5,587,459.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

RCE

By the enclosure, the applicant has requested entry of this amendment and response and have further requested removal of the finality of the outstanding official action. Per the enclosed Request for Continued Examination form, the USPTO is authorized to charge the associated fees to the undersigned firm's USPTO Deposit Account No. 03-03975.

Additional Fee

Although the applicant believes additional fees (beyond those presented herein) are not necessary for entry and consideration of this amendment/response, should the USPTO determine additional fees are due (for such consideration), the Patent Office is authorized to charge such fees to USPTO Deposit Account No. 03-3975.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §103(a)

The examiner has maintained the rejection of claims 16 and 17, and has newly rejected claims 23-27 under 35 U.S.C. §103(a) as allegedly being obvious over Demidem *et al.*, *Cancer Biother. Radiopharm.*, 12:177-186 (1997) (hereafter "Demidem") in view of Hagenbeek *et al.*, *J. Clin. Oncol.* 16:41-47 (1998) (hereafter "Hagenbeek") and Reff *et al.*, *Blood* 83:435-445 (1994) (hereafter "Reff"). The examiner also maintained the rejection of claims 16 and 17, and has newly rejected claims 23-27 under 35 U.S.C. §103(a) as allegedly being obvious over Davis *et al.*, *Clinical Cancer Research* 6:2644-2652 (2000) (hereafter "Davis") in view of Taji *et al.*, *Jpn. J. Cancer Res.* 89:748-756 (1998) (hereafter "Taji"). In view of the foregoing remarks, the applicant respectfully traverses.

Demidem in view of Hagenbeek and Reff

Applicant notes that a *prima facie* case of obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. M.P.E.P. §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, the prior art must provide some teaching, suggestion or motivation to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The applicant maintains his arguments previously submitted May 10, 2005. Briefly, the applicant reiterates that Demidem fails to teach each and every element of the present invention even when combined in view of Hagenbeek and Reff. Demidem only teaches that the murine chimeric antibody C2B8 sensitized DHL-4 B cell lymphoma cell line cells by a possible modulation of the anti-apoptotic response or by an inhibition of protective proteins to allow certain cytotoxic agents to be effective against the B cell lymphoma cells. The applicant submits that nowhere in the teachings of Demidem is there a discussion or suggestion of using an anti-CD20/IFN-α-2a fusion protein as a single vehicle for targeting

cell mediated cytotoxicity of B-cell lymphoma cells via the subject's own natural killer cells and/or macrophages.

Similarly, Hagenbeek and Reff do little to overcome the failings of Demidem. Hagenbeek teaches that IFN can be used as a maintenance treatment measure to prolong the time of re-progression of B cell lymphoma cells after chemotherapy, whereas Reff teaches using plasmid constructs to create chimeric anti-CD20 antibodies. Neither Hagenbeek nor Reff teach or suggest targeting tumor target cells expressing CD20 or using a fusion protein immunoconjugate comprising an anti-CD20 antibody or fragment thereof and a non-related IFN-α-2a protein component. Thus, Demidem, either alone or in combination with Hagenbeek and Reff, neither teach nor suggest the applicant's claimed invention. Without such teaching or suggestion, the examiner has not established a *prima facie* case of obviousness.

The examiner asserts that Demidem teaches that the anti-CD20 antibody, rituximab, enhances apoptosis of B cell lymphoma cell line cells, mediates antibody dependent cell-mediated cytotoxicity *in vitro*, and sensitizes B cell lymphoma cell line cells to cytotoxic drugs upon pretreatment with the anti-CD20 antibody. The examiner acknowledges that Demidem does not teach IFN-α-2a as one of the cytotoxic drugs. However, the examiner alleges that Hagenbeek teaches one how to make and purify human recombinant IFN-α-2a, and that IFN-α-2a has a good effect for patients with stage III and IV low-grade malignant NHL. Lastly, the examiner alleges that Reff teaches one of ordinary skill in the art how to construct a fusion protein comprising an anti-CD20 antibody or a fragment thereof fused at its carboxy terminus to IFN-α-2a via Figures 1 and 2. The examiner asserts that these figures "teach many useful restriction sites that could be used to fuse the human recombinant IFN-α-2a." Based on these three references, the examiner alleges that it would have been obvious to one of ordinary skill in the art to make and use an anti-CD20 antibody/IFN-α-2a fusion in the method of enhancing apoptosis in B cell lymphoma. The examiner further asserts that this fusion anti-CD20 antibody can thereby be used to treat lymphoma with a reasonable expectation of success since Hagenbeek teaches how to make recombinant IFN-α-2a and Reff teaches how to construct an anti-CD20 antibody construct. The examiner alleges that the skilled artisan would have been motivated to make a fusion protein to minimize the painful injection by giving one injection (rather than two), and by purifying one protein (as opposed to two), thereby reducing cost, saving time and minimizing pain.

The applicant points out to the examiner the following: 1) Hagenbeck does not teach how to make or purify recombinant IFN-α-2a; and 2) Reff does not teach how to construct a

fusion protein of an anti-CD20 antibody or a fragment thereof fused at its carboxy terminus to IFN-α-2a. First, in the Patients and Methods section of Hagenbeck (page 42, second column, 2nd full paragraph), IFN-α-2a was purchased from Hoffman-La Roche; making or purifying IFN-α-2a is neither taught nor disclosed in Hagenbeek. Next, as the applicant has stated in his response dated May 10, 2005, Reff teaches using plasmid constructs to create ***chimeric*** anti-CD20 antibodies. Figures 1 and 3 disclose restriction endonuclease sites which can be used to replace/insert light and heavy chain variable and constant regions from either human or mouse to create a ***chimeric*** mouse/human anti-CD20 antibody.

Combining these three references and their teachings, one of ordinary skill in the art would obtain a ***chimeric*** anti-CD20/IFN-α-2a antibody to reduce B cell proliferation and viability. There is no expectation of success for a ***chimeric*** anti-CD20/IFN-α-2a antibody to reduce B cell proliferation and viability *in vitro* or *in vivo*. Hagenbeek does not motivate one of ordinary skill to use IFN-α-2a as fusion partner of anti-CD20 antibody. In the Hagenbeek study, Habenbeck concluded that IFN-α-2a treatment "increased TTP (time to progression) **at the borderline of statistical significance**." *See* Hagenbeek, conclusion of the abstract (emphasis added). Hagenbeck further concluded that IFN-α-2a maintenance treatments did not influence the overall survival of patients suffering from low-grade malignant non-Hodgkin's lymphoma. *Id.* Based on this, one of ordinary skill in the art would not have been motivated to combine the teachings of Demidem with Hagenbeek and Reff because there was not a reasonable expectation of success.

Because the references do not 1) suggest or motivate one of ordinary skill in the art to modify the references or to combine the reference teachings, 2) teach all elements of the applicant's claimed invention when combined, and 3) suggest to one of ordinary skill in the art that combining the teachings of the reference would be successful, the examiner has failed to establish a *prima facie* case of obviousness. In view of the foregoing remarks, the applicant respectfully submits that the rejection of claims 16 and 17 and 23-27 under 35 U.S.C. §103(a) over Demiden in view of Hagenbeek and Reff is improper and should be withdrawn.

Davis in view of Taji

With regard to Davis in view of Taji, the applicant maintains his argument previously submitted May 10, 2005. Briefly, the applicant submits that Davis fails to teach each and every embodiment of the present invention even when combined in view of Taji. Davis teaches the separate administration of an anti-CD20 antibody and IFN-α-2a to modulate B

cell lymphoma, whereas the applicant's method uses a fusion protein, which simultaneously targets B-cell lymphoma cells as well as uses the subject's effector cells to kill the targeted B-cell lymphoma cells. The anti-CD20 antibody of Davis is not fused to IFN-α-2a, and therefore would not specifically target IFN-α-2a to a tumor cell. In addition, the applicant's method of enhancing apoptosis of target cells efficiently uses a 1:1 ratio of anti-CD20 antibody or fragments thereof with IFN-α-2a.

Similarly, Taji does little to overcome the failings of Davis. Taji teaches using a chimeric anti-CD20 antibody (consisting of human immunoglobulin G 1-κ constant regions and variable regions from murine anti-CD20 antibody) to study this chimeric antibody's role in inducing apoptosis to inhibit B-cell lymphoma cell lines. The applicant asserts that Davis in view of Taji neither teaches nor suggests the applicant's claimed invention. Accordingly, without such teaching or suggestion, the examiner has not established a *prima facie* case of obviousness.

Contrary to the examiner's assertions, the applicant submits that there is no reasonable expectation of success to enhance apoptosis using the teachings of Davis in view of Taji. The examiner alleges that Davis teaches the administration of anti-CD20 and IFN-α-2a has a synergistic effect, while Taji teaches that anti-CD20 antibody treatment enhances apoptosis of B cell lymphoma cell lines. Taken together, the examiner argues that it would have been obvious to one of ordinary skill in the art to make and use an anti-CD20 antibody or antibody fragment fused at its carboxy terminus to IFN-α-2a to enhance apoptosis in B cell lymphoma.

The applicant respectfully disagrees with the examiner. The examiner appears to overstate the teachings of Davis. Davis does not teach that anti-CD20 antibody and IFN-α-2a have a synergistic effect. Davis specifically states, "the potential 10.1 month increase in TTP observed with combination therapy, compared with the TTP observed with single-agent rituximab treatment, is **not currently statistically significant**. Definitive conclusions regarding the potential benefits of combination therapy require a randomized trial investigating single agent treatment *versus* combination therapy." *See* Davis, page 2650, 1st column, last paragraph (emphasis added). Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of Davis in view of Taji because there was not a reasonable expectation of success. Furthermore, any suggestion, teaching or motivation arising from Davis teaches only the sequential administration of an anti-CD20 antibody and IFN-α-2a, not the simultaneous administration as taught by the present invention. Davis specifically reported that "rituximab and IFN were **not to be administered on the same**

day." *See* Davis, page 2645, Figure 1 legend (emphasis added). Taji teaching of a chimeric anti-CD20 antibody does nothing to overcome Davis' failure to simultaneously administer anti-CD20 antibody and IFN-α-2a. Thus, Davis in view of Taji does not establish a *prima facie* case of obviousness as asserted by the examiner.

In view of the foregoing remarks, the applicant respectfully submits that the rejection of claims 16-17 and 23-27 under 35 U.S.C. §103(a) over Davis in view of Taji is improper and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §112

On page 10 of the official action, the examiner rejected claim 25 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the specifically recited antibodies. The examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with this claim.

Amended claim 25 is directed to the method of claim 16, wherein said immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof selected from the group consisting of rituximab (RITUXAN®), 1F5 (ATCC No. HB-9645; copy enclosed in Appendix A), ibritumomab (ZEVALIN®) and anti-B1 (BEXXAR®) antibodies. The applicants submit that the specification and claims have been amended to either identify the ATCC accession number for the 1F5 (ATCC No. HB-9645) antibody or the registered name for ibritumomab (ZEVALIN®) and anti-B1 (BEXXAR®) antibodies. Because these are commercially available antibodies, the public can readily obtain the antibodies of claim 25 by using the ATCC accession number and the registered names.

With respect to the 1H4 antibody, the applicant submit that Haisma *et al.* (1998) *Blood* 92(1):184-190 discloses the entire nucleotide and amino acid sequence of the variable heavy and light chains of 1H4. *See* Haisma *et al.*, Figure 3, a copy of which is also enclosed in Appendix B. Therefore, one of ordinary skill in the art would be capable of obtaining the 1H4 antibody using the Haisma reference. The applicant notes that the Haisma reference has been incorporated in its entirety within the instant specification and further notes that the Haisma reference is available online to the public without cost. The applicant respectfully submits that every antibody referenced in claim 25 is readily available to the public or alternatively, obtainable based on information within the specification. Accordingly, the specification fully enables the invention of amended claim 25.

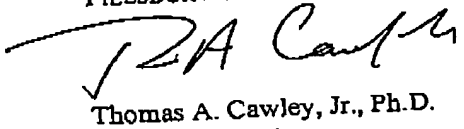
In view of the foregoing remarks and amendment, the applicant respectfully submits that the rejection of claim 25 under 35 U.S.C. §112, first paragraph, for lack of enablement, is improper and should be withdrawn.

IV. CONCLUSION

In view of the foregoing, the claims are now believed to be in form of allowance, and such action is hereby solicited. If any point remains which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number below.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP



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